REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

I. CLAIM STATUS & AMENDMENTS

Applicants hereby acknowledge that the Examiner has maintained the election of species requirement and made such requirement final. As indicated in the Office Action Summary, claims 1-3, 6, 9-14, 16, and 31 have been examined and claims 4, 5, 7, 8, 15, and 17-30 have been withdrawn from consideration as being drawn to a non-elected invention. Applicants hereby acknowledge that the restriction requirement is maintained and made final.

By the foregoing, claim 1 has been amended, at lines 1-2, to recite "[a] method of therapeutically treating, prophylactically treating or ameliorating atopic dermatitis . . . ." Support for this amendment can be found throughout the originally filed application, including for example on at least page 9, lines 28-35, and in original claim 16. Claim 1 has also been amended at lines 26-27 to correct an inadvertent typographical error. Claim 6 has also been amended to depend from claim 4, instead of claim 5 which has been withdrawn from consideration. No new matter has been introduced by the present amendments to the claims.

II. INFORMATION DISCLOSURE STATEMENTS

Applicants acknowledge receipt of the Examiner-initialed copies of the Information Disclosure Statements ("IDSs") submitted on April 16, 2002 and on June 7, 2002. However, the Examiner has not yet returned Examiner-initialed copies of the IDSs submitted on November 14, 2002 and on March 8, 2002. For the Examiner's convenience, enclosed herein are copies of the PTO-1449 forms previously submitted with the noted IDS. Applicants respectfully request that the Examiner consider the references cited therein and return Examiner-initialed copies of these IDSs to the Applicants.

III. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1-3, 6, 9-14, and 31 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for treating or ameliorating specific exemplified skin diseases using nitroimidazole derivatives, does not allegedly provide an enabling disclosure for treating or ameliorating all skin diseases. See July 16, 2003 Official Action at 2-3.

Applicants respectfully traverse this rejection. Nonetheless, for the sole purpose of expediting prosecution and not to acquiesce to the rejection, claim 1 has been amended to recite "[a] method of therapeutically treating, prophylactically treating or ameliorating atopic dermatitis . . . ." The present amendment obviates the rejection since the Examiner has affirmatively stated that the specification is "enabling for treating or ameliorating specific examplified skin diseases . . . such as atopic dermatitis. See July 26, 2003 Official

Action at 2. This is further supported by the fact that claim 16, which is directly dependent on claim 1 and recites that the skin disease is atopic dermatitis, was not included in the present rejection. Accordingly, Applicants respectfully request the withdrawal of this rejection.

IV. REJECTION UNDER 35 U.S.C. § 102

Claims 1-3, 6, 9-14, and 31 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Goodman et al. WO98/027960 ("Goodman"). See July 16, 2003 Official Action at 4. Applicants respectfully traverse this rejection.

Applicants submit that the cited art reference fails to anticipate the amended claims because the reference fails to disclose **each** and **every** element of the claimed invention. To anticipate a claim, a single prior art reference must teach, either expressly or inherently, each and every element of the claimed invention. See M.P.E.P. § 2131; Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987); Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1379, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986).

Currently pending claim 1 recites "[a] method of therapeutically treating, prophylactically treating or ameliorating atopic dermatitis . . . ." Goodman on the other hand fails to teach the treatment of "atopic dermatitis." Applicants note that claim 16, which also recites "atopic dermatitis," was not included in the present rejection. Furthermore, the Examiner at page 5, lines 8-10 of the July 16, 2003 Official Action

acknowledged that the Goodman reference (*i.e.*, WO98/027960) fails to teach treating atopic dermatitis. Thus, in view of the above, Applicants respectfully request withdrawal of this rejection.

V. REJECTION UNDER 35 U.S.C. § 103

Claims 12-13 and 16 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Goodman et al. WO98/027960 ("Goodman") in view of Miller et al., JOURNAL OF IMMUNOPHARMACOLOGY, Vol. 2, Part. 2, pp.225-243 (1980) (only the Abstract is cited) ("Miller") and Fleischer, JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, Vol. 104 (3, Pt. 2) pp. S126-S130 (1999) (only the Abstract is cited). See July 16, 2003 Official Action at 5-6. Applicants respectfully traverse this rejection.

Applicants respectfully submit that a proper *prima facie* case of obviousness against the claimed invention has not been made. To establish a *prima facie* case of obviousness, three criteria must be met. First, the prior art references must teach or suggest each and every element of the claimed invention. See M.P.E.P. § 2143.03; In re Royka, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974); In re Zurko, 111 F.3d 887, 888-89, 42 U.S.P.Q.2d 1476, 1478 (Fed. Cir. 1997); In re Wilson, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

Second, there must be some suggestion or motivation in the references to either modify or combine the reference teachings to arrive at the claimed invention. See M.P.E.P. § 2143; In re Vaeck, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). This

element requires that an objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references to arrive at the claimed invention. In re Fine, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). In other words, the Examiner must provide a logical reason as disclosed in the prior art at the time of the invention for combining the references along the lines of the invention. Otherwise, the use of such teachings as evidence of non-obviousness will entail impermissible hindsight. Ex parte Stauber, 208 U.S.P.Q. 945, 946 (Bd. App. 1980).

Third, the prior art must provide a reasonable expectation of success. See M.P.E.P. § 2143.02; Vaeck, 947 F.2d at 488, 20 U.S.P.Q.2d at 1438; In re Merck & Co., Inc., 800 F.2d 1091, 231 U.S.P.Q. 375 (Fed. Cir. 1986).

As to the first required element for establishing a *prima facie* case of obviousness, Applicants submit that the prior art fails to teach using nitroimidazole derivatives to treat atopic dermatitis. As discussed above, the Examiner acknowledges that Goodman fails to teach the treatment of atopic dermatitis. According to the Examiner, Goodman teaches the treatment of inflamed skin diseases such eczema using tinidazole via topical application. Thus, the Examiner relies on Fleischer and Miller for the suggestion to treat atopic dermatitis.

Fleischer and Miller, however, fail to remedy this serious deficiency of Goodman. In particular, Fleischer and Miller fail to teach and/or suggest the treatment of atopic dermatitis with a reasonable expectation of success. Regarding Fleischer, the Examiner

believes that this reference teaches a treatment of atopic dermatitis. Specifically, the Examiner asserts:

> Fleischer (1999) teaches a treatment of atopic dermatitis which is a chronic and relapsing form of eczema where immune regulation appears to play an important role in the cause of atopic dermatitis and immunosuppressants are effectively used in the treatment of atopic dermatitis, see entire abstract.

See July 16, 2003 Official Action at 5, ll. 11-14. However, the position that "immune regulation appears to play an important role in the cause of atopic dermatitis" is incorrect. In this regard, Fleischer recognizes that "immune dysregulation appears to play an important role in the cause of atopic dermatitis." See Fleischer, Abstract, ll. 4-5. Thus, according to the cited art, immune dysregulation, not immune regulation as postulated by the Examiner, plays the important role.

Furthermore, Fleischer describes:

> Topical corticosteriod agents have been the mainstay of therapy for atopic dermatitis because of their broad immunomodulatory effects. However, topical corticosteriod agents are not ideal agents because when used over the long term, they may cause cutaneous atrophy and immunosuppression.

See Fleischer, Abstract, ll. 6-10. Fleischer therefore indicates that topical corticosteriod agents having broad immunomodulatory effects have been used for the treatment of atopic dermatitis. However, topical corticosteriod agents are not good for this purpose because they cause adverse effects such as immunosuppression.

Given such circumstances, Fleischer tried to find another effective agent for the treatment of atopic dermatitis, *i.e.*, tacrolimus. In this connection, Fleischer describes:

> Systemic corticosteridal agents, certain antihistaminic agents, systemic cyclosporin, and phototherapy have proven value in treating patients with

> atopic dermatitis. In the search for a noncorticosteriodal topical agent, tacrolimus stands out as being uniquely suited for this condition. Tacrolimus affects a broad spectrum of inflammatory mediators and processes known to be relevant to atopic dermatitis pathogenesis.

See Fleischer, Abstract, lines 10-17. Thus, Fleischer indicates that tacrolimus is an effective agent for the treatment of atopic dermatitis since tacrolimus affects a broad spectrum of inflammatory mediators and processes known to be relevant to atopic dermatitis pathogenesis. However, Fleischer never indicates that tacrolimus is an effective agent for the treatment of atopic dermatitis due to its immunosuppression activity. Furthermore, although tacrolimus is a known immunosuppressant, Fleischer never indicates or suggests that any other immunosuppressant agent can be effective for the treatment of atopic dermatitis. Thus, Fleischer fails to provide the requisite motivation and/or suggestion to use tinidazole derivatives to treat atopic dermatitis.

In addition, the chemical structure of tacrolimus, which is a metabolite from Strephtomyces tsukubaensis, is completely different from that of tinidazole.[1] Since

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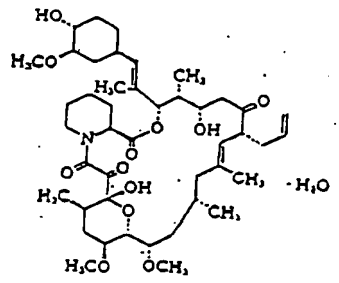
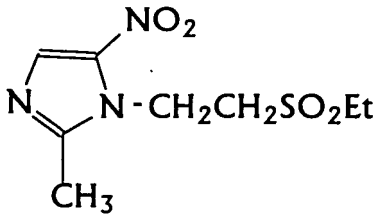
[1] The chemical structures of Tacrolimus and Tinidazole are as follows:

(I) Tacrolimus



(II) Tinidazole



tacrolimus is greatly different from tinidazole in its chemical structure and Fleischer never suggests its use to treat atopic dermatitis, those skilled in the art would not believe that tinidazole has the same functions as those of tacrolimus. Consequently, Fleischer fails to provide a reasonable expectation of success of using tinidazole to treat atopic dermatitis.

Furthermore, even if the Examiner maintains that tacrolimus is suggestive for the use of tinidazole in the treatment of atopic dermatitis, which it was not, the use of tinidazole provides surprising and unexpected results. It is well established that surprising and unexpected results are indicia of non-obviousness. See Fromson v. Advance Offset Plate, Inc., 755 F.2d 894, 904 (Fed. Cir. 1988). Subsequent to Applicants' July 14, 2000, international filing date, it was found that tacrolimus ointment cannot be used for the treatment of atopic dermatitis in patients with a high level nephropathy of hyperkalemia; in pregnant women or women suspecting pregnancy; and in patients receiving UV therapy such as PUVA therapy. Furthermore, as a rule, the tacrolimus ointment is not used for patients of dermal infectious diseases. By contrast, the present invention has none of these above-mentioned defects, and can be used to treat the patients listed above. Thus, even if the Examiner maintains that tacrolimus is suggestive tinidazole in the treatment of atopic dermatitis, which is it was not, the claimed invention clearly achieves surprising and unexpected results that are indicative of non-obviousness.

Miller also fails to provide the requisite motivation and/or suggestion to use tinidazole derivatives to treat atopic dermatitis. With regard to Miller, the Examiner has acknowledged that this reference teaches tinidazole as an effective in vivo

immunosuppressant. See July 17, 2003 Official Action at 5, ll. 15-16. However, Miller describes:

> Two compounds, clotrimazole and dacarbazine (DTIC) produced a dose related suppression of these responses. . . .[W]hereas metronidazol and tinidazole actually enhanced the response . . . . It is suggested that experiments of this kind are helpful in identifying those imidzaole [sic] compounds that could be used as immunosuppressant in vivo.

See Miller, Abstract, ll. 3-9 (emphasis added). In this regard, Miller teaches experiments of this kind are helpful in identifying whether imidazole compounds can be used as in vivo immunosuppressants. Miller does not expressly teach that tinidazole can be used as an in vivo immunosuppressant. Nor does Miller teach that tinidazole is useful for the treatment of atopic dermatitis. Even if the Examiner believes that Miller teaches that tinidazole can be used in vivo as immunosuppressant, those skilled in the art would not be able to arrive at the claimed invention in view of this teaching due to the great difficulty in treating atopic dermatitis as discussed above. Thus, Miller also fails to provide the requisite motivation and/or suggestion to use tinidazole derivatives to treat atopic dermatitis. Consequently, Miller also fails to provide a reasonable expectation of success of using tinidazole to treat atopic dermatitis.

Because the combination of Goodman in view of Fleischer and Miller does not teach and/or suggest each and every element of the claimed invention and because there is no motivation to combine these references to arrive at the claimed invention, Applicants submit that the cited references do not, and indeed cannot, render the claimed invention

obvious. Thus, for the above-stated reasons, Applicants respectfully request the withdrawal of the rejection of claims 12-13 and 16 under 35 U.S.C. § 103(a).

CONCLUSION

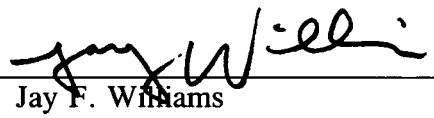
From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned attorney so that prosecution of the application may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

Date: October 16, 2003

By: 

Jay F. Williams
Registration No. 48,036

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

ATTACHMENT

Substitute for form 1449A/PTO

SECOND INFORMATION DISCLOSURE STATEMENT BY APPLICANT

ATTORNEY'S DKT NO.	APPLICATION NO.
018995-452	10/046,575
APPLICANT: Nishizumi NISHIMUTA et al.	
FILING DATE: January 16, 2002	GROUP: 1614

U.S. PATENT DOCUMENTS

Examiner Initials	U.S. Patent Document Number	U.S. Patent Document Kind Code (if known)	Name of Patentee or Applicant of Cited Document	Date of Publication (MM-DD-YYYY)

FOREIGN PATENT DOCUMENTS

Examiner Initials	Foreign Patent Document Number	Foreign Patent Document Kind Code (if known)	Country	Date of Publication (MM-DD-YYYY)	Translation Yes	Translation no

NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Include name of author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.
	KOSTAKIS et al., "The Immunosuppressive Action of Metronidazole," *IRCS Medical Science*, 1977, p. 142, Vol. 5.
	Pharmacy, 1996, pp. 1137-1141, Vol. 47, No. 8.

Examiner Signature		Date Considered	

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. SEND TO: Assistant Commissioner for Patents, Washington, D.C. 20231.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

ATTORNEY'S DKT NO.	APPLICATION NO.
018995-452	10/046,575
APPLICANT: Nishizumi NISHIMUTA et al.	
FILING DATE: January 16, 2002	GROUP: Unassigned

U.S. PATENT DOCUMENTS

Examiner Initials	U.S. Patent Document Number	U.S. Patent Document Kind Code (if known)	Name of Patentee or Applicant of Cited Document	Date of Publication (MM-DD-YYYY)

FOREIGN PATENT DOCUMENTS

Examiner Initials	Foreign Patent Document Number	Foreign Patent Document Kind Code (if known)	Country	Date of Publication (MM-DD-YYYY)	Translation Yes	Translation no
	98/27960	A2	WO	07-02-1998		
	89/06537	A1	WO	07-27-1989		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Include name of author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.

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